



Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Herpes Simplex Virus Infections (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations

- HIV-infected patients should use male latex condoms consistently and correctly during sexual intercourse to reduce the risk of exposure to herpes simplex virus (HSV) and other sexually transmitted pathogens (**AI***). They should specifically avoid sexual contact when herpetic lesions (genital or orolabial) are evident (**AIII**).
- Although use of acyclovir or valacyclovir, beginning at 36 weeks of pregnancy to reduce the need for cesarean delivery, is recommended in HIV-uninfected women with recurrent genital herpes, data are insufficient to make a specific recommendation for HIV and HSV coinfecting women (**BIII**).
- For pregnant women who have active genital HSV lesions at the onset of labor, delivery by elective cesarean delivery, preferably before rupture of membranes, is recommended (**BII***).
- Acyclovir is the drug of choice for treatment of local and disseminated HSV in infants and children, regardless of HIV-infection status (**AI**).
- Neonatal HSV disease should be treated with high-dose intravenous (IV) acyclovir (20 mg/kg body weight), administered for 21 days for central nervous system (CNS) and disseminated disease and for 14 days for disease of the skin, eyes, and mouth (**AI**). IV acyclovir therapy should not be discontinued in neonates with CNS disease unless a repeat cerebrospinal fluid HSV DNA polymerase chain reaction assay is negative near the end of treatment (**BIII**). Oral acyclovir prophylaxis for 6 months after treatment of neonatal disease involving the CNS or skin, eyes, and mouth can prevent cutaneous recurrences and may be associated with superior neurodevelopmental outcome in those with CNS disease (**AI**).
- Beyond the neonatal period, HSV encephalitis should be treated with IV acyclovir for 21 days (**AIII**).
- First-episode orolabial or genital lesions in HIV-infected children or adolescents can be treated with oral acyclovir for 7 to 10 days (**AI**). Children or adolescents with severe immunosuppression and moderate-to-severe mucocutaneous HSV lesions should be treated initially with IV acyclovir and may require longer therapy (**AI***).
- Recurrent mucocutaneous lesions, if treated, are generally treated with oral acyclovir for 5 days (**AI***).
- Alternatives to oral acyclovir in adolescents and adults include valacyclovir and famciclovir (**AI***).
- Patients with acute retinal necrosis should receive combination antiretroviral therapy and high-dose IV acyclovir for 10 to 14 days, followed by prolonged (i.e., 4–6 weeks) oral therapy, such as valacyclovir or acyclovir (**AIII**).
- HSV keratoconjunctivitis is usually treated with topical trifluridine or oral acyclovir alone, although many experts recommend the combination (**AII***).
- The treatment of choice for acyclovir-resistant HSV is IV foscarnet (**AI***).
- Children or adolescents who have frequent or severe orolabial or genital recurrences can be given daily suppressive therapy with oral acyclovir (**AI***). Valacyclovir and famciclovir also are options for adolescents (**AI***).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Herpes simplex virus type 1 (HSV-1) and HSV-2 can cause disease at any age. HSV-1 is transmitted primarily through contact with infected oral secretions; HSV-2 is acquired primarily through contact with infected genital secretions. In the United States, HSV-1 seroprevalence in children increases from about 30% at ages 6 to 13

years to 39% in adolescence and is higher among children who live below the poverty level compared to those who live at or above poverty level.^{1,2} Seroprevalence in children is higher in non-Hispanic blacks and in those born in Mexico. The seroprevalence of HSV-1 approaches 60% in older adults.² HSV-2 seroprevalence prior to reported sexual debut is low (2.6%) and rises to 22% to 26% in 30- to 49-year-olds and is higher in non-Hispanic blacks, individuals with large numbers of sex partners, females, and in those living below the poverty level.² HSV-2 seroprevalence is higher among individuals who were age 17 years or younger compared with 18 years or older at time of sexual debut.² Among young adolescent girls, a longer period of sexual activity and having had another sexually transmitted disease in the past 6 months was associated with HSV-2 seropositivity.³ Among some populations of older adolescents and young adults, HSV-1 is the cause of a large proportion of first episodes of genital HSV infection.⁴⁻⁶ These epidemiologic data indicate that children are at significant risk for primary infection or reactivation with HSV throughout childhood and adolescence. The age-specific seroprevalence of both HSV types is higher in many developing countries.

Young children generally acquire HSV-1 from oral secretions of caretakers or playmates. Rarely is this the result of contact with active herpetic lesions; infection most often results from exposure to HSV shed asymptomatically in the saliva of the contact. Salivary shedding of HSV detected by polymerase chain reaction (PCR) in HSV-1-seropositive adults is frequent (9% of days).^{7,8} While older individuals may acquire HSV-1 in this manner, HSV-1 also can be acquired via sexual activity in adults who were not infected earlier during childhood or adolescence. HSV-2 is more likely to be acquired during adulthood or adolescence, rather than childhood, as it is typically sexually transmitted. Genital shedding of HSV-2 by HSV-infected women who are not HIV-infected, as detected by PCR, is very frequent (19% of days).⁸ Either virus type can be spread by oral-oral, oral-genital, and genital-genital contact. In general, shedding of oral HSV persists longer in young children. Oral and genital HSV shedding are more common both in close proximity to the first episode of infection and also in HIV-infected patients. HSV infection can be acquired as a neonatal infection, primarily through exposure to HSV-infected maternal fluids during vaginal delivery; less commonly, infection may occur *in utero*.⁹ Newborns also infrequently are infected from oral secretions of an adult caretaker. The risk of transmitting HSV during delivery is approximately 1% in pregnant women with remote primary HSV infection, whereas the risk is much higher for infants born to women with recent HSV infection (range: 30%–50%).⁹ Maternal HSV antibody status before delivery likely influences the probability of transmission to infants and the severity of neonatal infection.^{10,11} Genital shedding of HSV at delivery increases the risk of transmission, as does prolonged rupture of membranes (>6 hours), probably because of ascending HSV infection from the cervix. Importantly, mothers of neonates with HSV often do not provide a history of either past genital HSV infection or incident genital lesions.^{12,13}

Dual HSV and HIV infection of pregnant women is likely to be common, because both viral infections share risk factors (race, socioeconomic status, and number of sexual partners). Genital HSV was detected by PCR in 31% of HSV-seropositive, HIV-infected women at the time of delivery, compared with 9.5% of HSV-seropositive, HIV-uninfected pregnant women.¹⁴ Shedding is greatest when the CD4 T-lymphocyte count is low.¹⁵ In spite of the potential risk factors for the infant, there is no evidence that *in utero* HSV infection occurs more frequently in HIV-infected pregnant woman coinfecting with HSV-2 or that infants born to these women are at increased risk of perinatal (intrapartum) HSV infection. In the general population, the neonatal HSV infection rate is 1 case per 2,000 to 10,000 deliveries,^{9,16} indicating that neonatal HSV will rarely be observed at clinics caring for dually-infected pregnant women.

Conversely, numerous studies have shown that coinfection with genital HSV in adults is associated with higher titers of HIV RNA in plasma and genital secretions; HSV-seropositivity increases the risk of HIV transmission to sexual partners, even in the absence of genital ulcer disease.^{17,18} Three studies suggest that maternal HSV coinfection increases the risk of intrapartum HIV transmission.¹⁹⁻²¹

Clinical Manifestations

In most immunologically competent children, HSV infection causes minimal signs and symptoms and is usually not recognized as a distinct illness. Up to one third of children may develop a characteristic orolabial

syndrome (primary gingivostomatitis), usually associated with HSV-1 infection, which consists of fever, irritability, tender submandibular lymphadenopathy, and superficial, painful ulcers on the gingival and oral mucosa and perioral area.^{22,23} HSV viremia occurs in approximately one-third of patients with primary herpetic gingivostomatitis.²⁴ HSV is a common cause of severe posterior pharyngitis in older children and adolescents.²⁵ Children with advanced HIV infection may have primary infection with multiple lesions that are atypical in appearance and delayed in healing. Very rarely, disseminated HSV occurs with visceral involvement (including liver, adrenals, lung, and brain) and generalized skin lesions. Small crops of recurrent perioral vesicles (“cold sores”) that heal quickly can occur throughout life in both healthy and HIV-infected children, but those with AIDS are at risk of frequent recurrences, which can be associated with severe ulcerative disease and symptoms similar to primary infection.²⁶ HIV-infected children also may have prolonged shedding of HSV after both primary and reactivation infection. HSV esophagitis, which occurs in severely immunocompromised children, can result from failure to limit replication of HSV present in saliva, although a study of adults found that evidence of oral HSV infection often is not present simultaneously.²⁷ Prolonged cutaneous HSV infection and organ involvement are AIDS-indicator conditions. These illnesses are uncommon in the era of combination antiretroviral therapy (cART), with a documented incidence rate of systemic HSV of 0.14 per 100 child-years.²⁸

Genital infection is the most common manifestation of HSV-2 infection in sexually active adolescents. Most primary infections are asymptomatic or subclinical; however, when symptoms do occur, they are characterized by painful, ulcerative lesions on the perineum, penis, and vaginal and urethral mucosae. Mucosal disease often is accompanied by dysuria and/or vaginal or urethral discharge. Inguinal lymphadenopathy, particularly in primary infection, is common with perineal disease.²⁹ Frequent recurrences and delayed healing are more likely in severely immunosuppressed patients. Severe proctitis and perianal infection occur in patients who practice receptive anal intercourse.^{7,30}

In HIV-infected patients, HSV keratitis and herpetic whitlow are similar in presentation to diseases in HIV-uninfected individuals, but may be more severe. Acute retinal necrosis is a rare sight-threatening complication that occurs more frequently in immunocompromised individuals. HSV encephalitis occurs in HIV-infected patients, but is not more frequent or severe than in HIV-uninfected individuals and has similar signs and symptoms (encephalopathy, neurologic abnormalities/seizures, and mononuclear pleocytosis in cerebrospinal fluid [CSF]). Focal deficits and temporal lobe abnormalities on neuroimaging are typical.^{31,32}

Neonatal infection in infants born to dually-infected mothers is similar in presentation to that seen in HIV-uninfected infants. Neonatal HSV can appear as disseminated multiorgan disease; localized disease of the central nervous system (CNS); or disease localized to the skin, eyes, and mouth.³³ Vesicular rash occurs in only approximately 60% of infants with CNS or disseminated disease.^{33,34}

Diagnosis

Clinical diagnosis is based on the typical location and appearance of vesicles and ulcers. The virus is readily isolated in tissue culture within 1 to 3 days, especially when samples are from first episode infections or obtained soon after the appearance of recurrent lesions (especially when vesicles are present).^{35,36} Speed and accuracy are maximized with the shell vial method, which combines centrifugation and staining with fluorescein-conjugated monoclonal antibodies to detect synthesis of early HSV proteins, thereby providing an etiologic diagnosis after 24 hours. Detection of HSV DNA by PCR, which is very sensitive and specific, is the gold standard method for diagnosis of HSV infection. DNA PCR may be especially useful when assessing skin lesions that are recurrent or that are being evaluated long after their appearance. In these cases, the HSV DNA remains in the healing lesions, even though HSV can no longer be cultured. Direct immunofluorescence for HSV antigen can be performed on cells scraped from skin, conjunctiva, or mucosal lesions.³⁷ The sensitivity of this method may not exceed 75%, often because it is difficult to obtain evaluable specimens.

Detection of HSV DNA in the CSF is the preferred diagnostic test for evaluation of children with suspected HSV encephalitis, because cultures of CSF are usually negative. Sensitivity of HSV PCR is generally $\geq 95\%$ for

CSF, especially if obtained more than 3 days after onset of herpes encephalitis.^{32,38} During therapy for HSV-proven encephalitis, the CSF HSV PCR remains positive for a mean of 10 days after neurologic onset.³⁹ In neonatal CNS HSV disease, CSF PCR has a sensitivity of 75% to 100% and a specificity of 71% to 100%.³⁴

Specimens from newborns with suspected neonatal HSV should be obtained from blood, skin vesicles, mouth or nasopharynx, conjunctiva, and stool or rectum. Positive cultures obtained from any of these sites more than 48 hours after birth indicate viral replication rather than contamination after intrapartum exposure.

Definitive diagnosis of HSV esophagitis requires endoscopy with biopsy. Histologic evidence of multinucleated giant cells with intranuclear viral inclusions and positive staining with monoclonal antibodies supplement culture or PCR results.

The rapid onset of poor vision, red eye, or eye pain should result in an immediate referral to an ophthalmologist, because these may be caused by herpesviruses or other pathogens that require specialized diagnostic (including fluorescein staining to detect characteristic dendritic corneal ulceration and fundoscopic exam) and treatment approaches.

Typing of HSV isolates (or genotyping of amplicons) can provide important prognostic information, since recurrence frequency after genital HSV-1 infection in HIV-uninfected patients is significantly less than after HSV-2 infection.^{40,41}

Prevention Recommendations

Preventing Exposure

Exposure to HSV-1 is an inevitable part of childhood. Although avoiding direct contact with secretions from adult caretakers, siblings, or other close contacts with active herpes labialis is intuitive, it is likely that most infections occur as a result of unrecognized exposure to the frequent asymptomatic shedding of HSV by individuals with prior infection.

When used consistently and correctly, male latex condoms reduce the risk of genital herpes when the infected site is covered, although data for this effect are limited (see <http://www.cdc.gov/condomeffectiveness/latex.htm>).⁴² Data pooled from 6 prospective studies estimated the odds of HSV-2 acquisition with every sexual act as increased by 3.6%, 2.7%, and 0% when condoms were never used, sometimes used, or always used, respectively.⁴³ In another pooled analysis, individuals who always used condoms had a 30% lower risk of HSV-2 acquisition compared with those who never used condoms, and risk of HSV-2 acquisition increased steadily with each unprotected sex act.⁴² Some data suggest that condom usage decreases the acquisition of genital HSV-2 infection by women, but may not be protective for heterosexual men or against HSV-1 infection;⁴⁴ however, neither of the aforementioned pooled analyses detected such a difference between men and women.^{42,43} HIV-infected patients should use latex condoms consistently and correctly during sexual intercourse to reduce the risk of HSV and other sexually transmitted pathogens (**AI***). They should specifically avoid sexual contact when herpetic lesions (genital or orolabial) are evident (**AIII**); however, most genital herpes infections are transmitted by individuals unaware that they are infected. Chronic suppressive therapy with valacyclovir in individuals with genital herpes reduces HSV-2 transmission to susceptible heterosexual partners by 50%.⁴⁵ Use of suppressive antiviral drugs against HSV in HIV-infected adults receiving cART resulted in fewer symptomatic lesions than in HIV-infected patients receiving such prophylaxis without cART, but subclinical mucosal HSV-2 shedding was similar regardless of cART.⁴⁶

The rate of HSV transmission to fetuses and neonates of HIV-infected pregnant women coinfecting with HSV is unknown. Effective cART regimens may decrease, but not prevent, maternal genital HSV shedding and recurrence of genital lesions.⁴⁷

Use of acyclovir or valacyclovir near term suppresses genital HSV outbreaks and shedding in late pregnancy in HIV-uninfected women with recurrent genital herpes and reduces the need for cesarean delivery for

recurrent HSV.⁴⁸ Although the sample size was insufficient to determine the effect of prophylaxis on neonatal infection, it is recommended that HIV-uninfected pregnant women with recurrent genital herpes be offered suppressive antiviral therapy at or beyond 36 weeks' gestation.⁴⁹ The safety and efficacy of this strategy have not been evaluated in HIV/HSV coinfecting women, who may have less HSV-2-specific antibody and/or T-cell function and are more likely to have both symptomatic and asymptomatic reactivation of genital HSV. Although suppressive antiviral therapy in late gestation is likely to also have efficacy in HIV-seropositive women, data are insufficient to make a specific recommendation **(BIII)**.¹¹ Elective cesarean delivery, preferably before rupture of membranes, is recommended for HIV-infected and HIV-uninfected women who have active genital HSV lesions at the onset of labor **(BII*)**.⁵⁰⁻⁵³

Preventing Disease

Antiviral prophylaxis before or after exposure to HSV has been used successfully, but has not been studied in HIV-infected patients and is not recommended.

Treatment Recommendations

Treating Disease

Acyclovir is the drug of choice for treatment of local and disseminated HSV in infants and children, regardless of HIV-infection status **(AI)**. Neonatal HSV disease should be treated with high-dose intravenous (IV) acyclovir (20 mg/kg body weight three times a day) administered for 21 days for CNS and disseminated disease and for 14 days for disease of the skin, eyes, and mouth **(AI)**.⁵⁴ IV acyclovir therapy should not be discontinued in neonates with CNS disease unless a repeat CSF HSV DNA PCR assay is negative near the end of treatment **(BIII)**.

IV acyclovir is the drug of choice for disseminated HSV and HSV encephalitis beyond the neonatal period. Beyond the neonatal period, HSV encephalitis should be treated (10-20 mg/kg body weight three times a day) for 21 days **(AIII)**.

First-episode orolabial or genital lesions in HIV-infected children or adolescents can be treated with oral acyclovir for 7 to 10 days as indicated by the response to therapy **(AI)**.^{22,23} Children or adolescents with severe immunosuppression and moderate-to-severe mucocutaneous HSV lesions should be treated initially with IV acyclovir and may need longer therapy, adjusted to the rate and character of healing **(AI*)**. Patients can be switched to oral therapy after their lesions have begun to regress, and therapy continued until lesions have completely healed.

Recurrent mucocutaneous lesions, if treated, are generally treated with oral acyclovir for 5 days **(AI*)**. Patients in whom frequent or severe recurrences are an unacceptable burden may benefit from daily suppressive therapy with acyclovir **(AI*)**.

Alternatives to oral acyclovir in older adolescents and adults include valacyclovir and famciclovir **(AI*)**. Valacyclovir is a prodrug of acyclovir with improved bioavailability that is rapidly converted to acyclovir after absorption. Sufficient information exists to support the use of valacyclovir in children, especially given its two- to threefold improved bioavailability compared with acyclovir, at a dose of 20 to 25 mg/kg body weight administered 2 to 3 times a day.^{55,56} No pediatric formulation is available and valacyclovir can generally only be used for children old enough to swallow the large valacyclovir tablets, although crushed valacyclovir tablets can be used to make a suspension with good bioavailability.⁵⁷ The database on the pharmacokinetics and dosing of famciclovir in children is insufficient to make recommendations, and no pediatric preparation is available.⁵⁸ Because of their improved bioavailability, valacyclovir and famciclovir administration at higher doses for only 1 to 3 days often is sufficient to manage recurrent genital HSV infection in HIV-uninfected adults and oral infections in HIV-infected adults.⁵⁹

Treatment for acute retinal disease caused by HSV should be guided by an ophthalmologist. Patients with acute retinal necrosis should be on cART and receive high-dose IV acyclovir (10–15 mg/kg body weight IV

every 8 hours for 10–14 days), followed by prolonged (i.e., 4–6 weeks) oral therapy, such as with valacyclovir or acyclovir (**AIII**).⁶⁰ HSV keratoconjunctivitis is usually treated with topical trifluridine or acyclovir, although many experts recommend combination therapy (**AII***).⁶¹ Because of potential corneal toxicity of topical therapy, close follow-up by an ophthalmologist is recommended and the duration of therapy should be individualized.

Monitoring and Adverse Events (Including IRIS)

Primary toxicities of acyclovir are phlebitis (when administered IV), renal toxicity, nausea, vomiting, and rash. Toxicities are similar for valacyclovir. In infants receiving high-dose acyclovir for neonatal disease, the major side effect was neutropenia (defined as absolute neutrophil count $<1,000/\text{mm}^3$).⁵⁴ Significant nephrotoxicity was observed in 6% of patients. For infants and children receiving high-dose IV acyclovir, monitoring of complete blood counts (CBCs) and renal function is recommended at initiation of treatment and once or twice weekly for the duration of treatment, particularly in those with underlying renal dysfunction and who are receiving prolonged therapy. If possible, avoid other nephrotoxic drugs. IV acyclovir must be adequately diluted and administered slowly over 1 to 2 hours. Acyclovir is excreted primarily by the kidney; as a result, dose adjustment based on creatinine clearance is needed in patients with renal insufficiency or renal failure.

Anogenital HSV has been included by some investigators as a potential manifestation of immune reconstitution inflammatory syndrome, but this has not been validated by comparing the anogenital HSV incidence after cART with the incidence during a similar period prior to cART.

Managing Treatment Failure

Resistance of HSV to acyclovir occurs in 5% to 10% of immunocompromised patients.⁶² This reflects the fact that acyclovir is a virostatic drug and patients with inadequate HSV-specific cell-mediated immunity fail to rapidly clear the HSV infection. Resistance to antiviral drugs should be suspected if systemic involvement and skin lesions do not begin to resolve within 5 to 7 days after initiation of therapy, skin lesions are atypical in appearance, or satellite lesions appear after 3 to 4 days of therapy. If possible, a lesion culture should be obtained and, if virus is isolated, susceptibility testing performed to confirm resistance. This may be difficult to arrange and will involve significant delay. Thus, the decision to change therapy is often based on clinical observations. All acyclovir-resistant HSV strains are resistant to valacyclovir, and it is very rare that they are sensitive to famciclovir. The therapeutic choice for acyclovir-resistant herpes is foscarnet (**AI***).^{63,64} Foscarnet has significant nephrotoxic potential; up to 30% of patients experience increases in serum creatinine levels. It also causes serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) in many patients, and secondary seizures or cardiac dysrhythmias can occur. Abnormal liver transaminases and CNS symptoms can also occur. For patients receiving foscarnet, CBC, serum electrolytes, and renal function should be monitored twice weekly during induction therapy and once weekly thereafter. Infusing foscarnet after saline fluid loading can minimize renal toxicity. Doses should be modified in patients with renal insufficiency (see package insert).

IV cidofovir is used to treat patients with HSV resistant to acyclovir and foscarnet.⁶⁵ For disease limited to a small number of indolent, non-healing lesions, topical formulations of trifluridine, foscarnet, and cidofovir have been used successfully, although this will require local preparation, and prolonged application for 21 to 28 days or longer may be required.⁶⁶

Preventing Recurrence

Administration of oral acyclovir prophylaxis (suppressive therapy) for 6 months can prevent cutaneous recurrences of HSV after neonatal disease of the CNS or skin, eyes, and mouth and may be associated with superior neurodevelopmental outcome in those with CNS disease (**AI**).⁶⁷

Beyond the neonatal period, because recurrent episodes of mucocutaneous HSV disease can be treated successfully, chronic prophylaxis with acyclovir or other available antivirals against HSV is not required after

lesions resolve in most patients. Effective cART may decrease recurrences. Children who have frequent or severe recurrences (i.e., 4 to 6 severe episodes a year) can be given daily prophylaxis with oral acyclovir (AI*). Valacyclovir or famciclovir also are options for prophylaxis in adolescents (AI*). Because corneal clouding can occur as a result of the stromal reaction of recurrent keratoconjunctivitis, some ophthalmologists use acyclovir prophylaxis to reduce the frequency of recurrences. However, resistance to acyclovir has been reported in this circumstance in HIV-uninfected patients.

Discontinuing Secondary Prophylaxis

Patients receiving prophylactic therapy should be evaluated annually for the need to continue prophylaxis. Cessation of secondary prophylaxis will be determined by the level of immune reconstitution, frequency and severity of subsequent recurrences, and each individual's tolerance for recurrent episodes.

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Dosing Recommendations for Prevention and Treatment of Herpes Simplex Virus (HSV) Infections

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Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	None.	None.	Primary prophylaxis is not indicated.
Secondary Prophylaxis	<p><u>Mucocutaneous Disease:</u></p> <ul style="list-style-type: none"> • Acyclovir 20 mg/kg body weight/dose (maximum 800 mg/dose) by mouth BID <p><u>Suppressive Therapy After Neonatal Skin, Eye, Mouth, or CNS Disease:</u></p> <ul style="list-style-type: none"> • Acyclovir 300 mg/m² body surface area/dose by mouth TID for 6 months 	<p><u>Mucocutaneous Disease, For Adolescents Old Enough to Receive Adult Dosing:</u></p> <ul style="list-style-type: none"> • Valacyclovir 500 mg by mouth BID, or • Famciclovir 500 mg by mouth BID 	<p><u>Secondary Prophylaxis Indicated:</u></p> <ul style="list-style-type: none"> • Suppressive secondary prophylaxis can be considered for children with severe and recurrent mucocutaneous (oral or genital) disease <p><u>Criteria for Discontinuing Secondary Prophylaxis:</u></p> <ul style="list-style-type: none"> • After a prolonged period (e.g., 1 year) of prophylaxis, consider suspending prophylaxis and determine with the patient whether additional prophylaxis is necessary. Although level of immune reconstitution is a consideration, no specific CD4 threshold has been established.
Treatment	<p><u>Neonatal CNS or Disseminated Disease:</u></p> <ul style="list-style-type: none"> • Acyclovir 20 mg/kg body weight IV/dose TID for ≥21 days <p><u>Neonatal Skin, Eye, or Mouth Disease:</u></p> <ul style="list-style-type: none"> • Acyclovir 20 mg/kg body weight IV/dose TID for 14 days <p><u>CNS or Disseminated Disease in Children Outside the Neonatal Period:</u></p> <ul style="list-style-type: none"> • Acyclovir 10 mg/kg body weight (up to 20 mg/kg body weight/dose in children <12 years) IV TID for 21 days <p><u>Moderate to Severe Symptomatic Gingivostomatitis:</u></p> <ul style="list-style-type: none"> • Acyclovir 5–10 mg/kg body weight/dose IV TID. Patients can be switched to oral therapy after lesions have begun to regress and therapy continued until lesions have completely healed. <p><u>Mild Symptomatic Gingivostomatitis:</u></p> <ul style="list-style-type: none"> • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 7–10 days 	<ul style="list-style-type: none"> • Valacyclovir is approved for immuno-competent adults and adolescents with first-episode mucocutaneous HSV at a dose of 1 g/dose by mouth BID for 7–10 days; also approved for recurrent herpes labialis in children ≥12 years using two, 2 g doses by mouth separated by 12 hours as single-day therapy. 	<p><u>For Neonatal CNS Disease:</u></p> <ul style="list-style-type: none"> • Repeat CSF HSV DNA PCR should be performed on days 19 to 21 of therapy; do not stop acyclovir until repeat CSF HSV DNA PCR is negative.

Dosing Recommendations for Prevention and Treatment of Herpes Simplex Virus (HSV) Infections

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Indication	First Choice	Alternative	Comments/Special Issues
Treatment, continued	<p><u>Recurrent Herpes Labialis:</u></p> <ul style="list-style-type: none"> • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 5 days <p><u>For First-Episode Genital Herpes (Adults and Adolescents):</u></p> <ul style="list-style-type: none"> • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 7–10 days <p><u>Recurrent Genital Herpes (Adults and Adolescents):</u></p> <ul style="list-style-type: none"> • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 5 days <p><u>Children with HSV Keratoconjunctivitis:</u></p> <ul style="list-style-type: none"> • Often treated with topical trifluridine (1%) or acyclovir (3%) applied as 1–2 drops 5 times daily. Many experts add oral acyclovir to the topical therapy. <p><u>Children with ARN:</u></p> <ul style="list-style-type: none"> • For children old enough to receive adult dose, acyclovir 10–15 mg/kg body weight/dose IV every 8 hours for 10–14 days, followed by oral valacyclovir 1 g/dose TID for 4–6 weeks • As an alternative, oral acyclovir 20 mg/kg body weight/dose QID for 4–6 weeks after IV acyclovir for 10–14 days 	<ul style="list-style-type: none"> • Recurrent genital HSV can be treated with valacyclovir 500 mg BID for 3 days or 1 g by mouth daily for 5 days. • Immunocompetent adults with recurrent herpes labialis can be treated with famciclovir, 1 g/dose by mouth BID for 1 day. • Famciclovir is approved to treat primary genital HSV in immunocompetent adults at a dose of 250 mg/dose by mouth TID for 7–10 days. • Recurrent genital HSV is treated with famciclovir 1 g/dose by mouth BID at a 12-hour interval for 2 doses • Famciclovir is approved for use in HIV-infected adults and adolescents with recurrent mucocutaneous HSV infection at a dose of 500 mg/dose by mouth BID for 7 days. <p><u>Acyclovir-Resistant HSV Infection:</u></p> <ul style="list-style-type: none"> • Foscarnet 40 mg/kg body weight/dose given IV TID (or 60 mg/kg body weight/dose BID) should be administered slowly over the course of 2 hours (i.e., no faster than 1 mg/kg/minute). 	<ul style="list-style-type: none"> • There is no pediatric preparation of valacyclovir (although crushed capsules can be used to make a suspension) and data on dosing in children are limited; can be used by adolescents able to receive adult dosing. • There is no pediatric preparation of famciclovir and data on dosing in children are unavailable; can be used by adolescents able to receive adult dosing. <p><u>Alternative and Short-Course Therapy in Immunocompromised Adults with Recurrent Genital Herpes:</u></p> <ul style="list-style-type: none"> • Acyclovir 800 mg per dose by mouth BID for 5 days • Acyclovir 800 mg per dose by mouth TID for 2 days <p>Note: Consultation with an ophthalmologist experienced in managing herpes simplex infection involving the eye and its complications in children is strongly recommended when ocular disease is present.</p>

Key to Acronyms: ARN = acute retinal necrosis; BID = twice daily; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; HSV = herpes simplex virus; IV = intravenous; PCR = polymerase chain reaction; QID = four times daily; TID = three times daily